Appendix M-II-A. Objectives and Rationale of the Proposed Research

State concisely the overall objectives and rationale of the proposed study. Provide information on the specific points that relate to whichever type of research is being proposed. **Objectives:** 1) To assess the clinical response rate of SCH 58500 when given intratumorally (endobronchial or percutaneous) to patients receiving combination chemotherapy for three cycles. 2) To assess the safety of the combination of chemotherapy and SCH 58500. 3) To assess the biologic activity of SCH 58500, by confirming wild-type p53 gene expression, specific to SCH 58500 as measured by reverse transcription and polymerase chain reaction analysis of treated tumor tissue. **See clinical protocol in Appendix I. Rationale:** p53 mutation occurs in up to 45% of patients with non small cell lung cancer[1]. Restoration of p53 function by gene transfer in non-small cell lung cancer tumors that are p53 altered, in culture and animal models has resulted in suppression of tumor growth[2]. In man we have confirmed the ability to safely administer SCH 58500 by the intratumoral route of administration to patients with non-small cell lung cancer. We have also confirmed the ability to transfer the gene by measuring mRNA (RT-PCR) in post injection tissue samples. Inhibition of cell growth by SCH 58500 in combination with various anti-cancer agents was evaluated against non-small cell lung, head and neck, ovarian, liver, breast and prostate cell lines, which were either mutant or null for p53. For all cell lines and all chemotherapy drugs in vitro, greater inhibition of proliferation was observed when the chemotherapy and SCH 58500 were used together, than either alone.

Approximately 50% of NSCLC patients present with advanced, Stage IV disease and have a median survival of less than 24 weeks. Over the past 30 years, a number of active drugs and drug combinations have been developed and the use of chemotherapy in NSCLC has been intensively studied. While some clinical trials showed a trend toward improved survival, others failed to show that chemotherapy was more beneficial than best supportive care (BSC). Meta-analyses of the published literature[3-4], however, have demonstrated a benefit of chemotherapy over supportive care in prolonging survival . A recent meta-analysis of using individual patient data from 9387 patients in 52 randomized trials[5] concluded that modern regimens containing cisplatin were more effective in improving survival than supportive care for all subgroups of patients. However, the essential drugs necessary for this effect were not identified by the analysis.

Given the above pre-clinical data, the fact that the p53 gene can successfully be transferred by the intratumoral route in NSCLC patients, and the safety profile from preliminary phase I studies, further investigation is warranted. We plan to evaluate the combination of platinol, taxane and vinca containing chemotherapy regimens and the addition of SCH 58500, p53.